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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/716,580
Filing Date: November 18, 2003
Appellant(s): MOCIKAT, RALPH

Chuan Gao
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/4/2009 appealing from the Office action mailed 1/6/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is substantially correct. There appears to be a typographical error in the last line of the Status of Claims omitting claim 29. Claim 29 is mentioned as being under examination on line 2 in the Status of Claims, as rejected on line 5 in the Status of Claims, and is listed as one of the claims appealed in the Claims Appendix. For the purposes of clarification, Claim 29 is under appeal and was finally rejected in the Action mailed 1/6/2009.

(4) Status of Amendments After Final

The status of amendments contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Polack et al., "Gene construct and its use." US Patent 6,521,449 (19 February 2003, benefit to 12 September 1996).

Mucke et al., "Suitability of Epstein-Barr Virus-based episomal vectors for expression of cytokine genes in human lymphoma cells." (Gene Therapy. 1997 Feb;4:82-92).

Levy et al., "Enhancement of B cell lymphoma and tumor resistance using idiotype/cytokine conjugates." US Patent 6,099,846 (8 August 2000, benefit to 14 April 1995).

Gillies et al., "Recombinant antibody cytokine fusion proteins." US Patent 5,650,150 (22 July 1997, benefit to 7 November 1991)

Mocikat et al., "Unaltered immunoglobulin expression in hybridoma cells modified by targeting of heavy chain locus with an integration vector."(Immunology. 1995:84:159-163).

[1]Kardinal et al., "Innovation vectors for antibody chimerization by homologous recombination in hybridoma cells." Eur J Immunol. 1995 Mar; 25(3):792-797. Abstract only.

[2]Mocikat, EP 0675203 (published 4 October 1995) (machine translation into English).

[3]Mocikat, DE 4406512 (published 16 February 1995) (machine translation into English)

[4]Tao et al., "Idiotype/granulocyte-macrophage colony-stimulating factor fusion protein as a vaccine for B-cell lymphoma." (Nature. 1993 Apr 22;362(6422):755-8. Abstract only.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112, First Paragraph - Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-9 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claims are drawn to a vector for the expression of immunoglobulin-cytokine fusion proteins in malignant B cells comprising (a) a continuous region of at least 1.5 kb which is homologous to a region of the μ intron or the κ intron, (b) at least one DNA sequence encoding a constant region of an immunoglobulin or a part of the constant region, (c) a DNA sequence encoding a cytokine, and (d) a marker gene which is selectable in eukaryotic B cells and contains a functional enhancer region. A malignant B cell containing the vector is also claimed.

A review of the language of the claim indicates that these claims are drawn to multiple genera including: vectors encoding a generic genus of cytokine-immunoglobulin fusion proteins; vectors

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[1] Cited prior art in the written description rejection under 35 USC 112, first paragraph rejection.
[2] Cited prior art in the written description rejection under 35 USC 112, first paragraph rejection.
[3] Cited prior art in the written description rejection under 35 USC 112, first paragraph rejection. Also cited as a rebuttal evidentiary reference in response to Appellant's arguments in the 10/18/2007 non-final Office Action, at pp. 5-6, with regard to the rejection under 35 USC 102(e) as being anticipated by the '449 patent.
[4] Cited prior art in the written description rejection under 35 USC 112, first paragraph rejection.

comprising a generic genus of immunoglobulin structures; vectors comprising a genus of cytokines; vectors comprising a genus of marker genes; vectors comprising a genus of enhancers; vectors encoding a genus of unspecified nucleic acids that are homologous to a region comprising the Cμ or Cκ enhancer; vectors comprising a genus of generic bacterially compatible regulatory units; vectors comprising a generic DNA sequence from part of a constant region of an immunoglobulin; vectors comprising a genus of interleukins; vectors comprising a genus of interferons; vectors comprising a genus of colony-stimulating factors; vectors comprising a genus of lymphokines; vectors comprising a genus of growth factors; and vectors comprising unspecified homologous regions from the mu or kappa introns of any species.

Applicable prior art includes Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996) who teach a BC219-TNFα vector integrated into BL60 cells (EBV-positive human lymphoma cells) capable of expressing TNFα (column 9, lines 23-24; and Table 2). BL60 cells with integrated BC219GM-CSF and BC216-IL6 expressing GM-CSF and IL-6 respectively, are also taught in Table 2.

Mucke et al., (Gene Therapy. 1997 Feb;4:82-92), teach vectors comprising gene constructs of cytokine fusion proteins expressed in malignant B-cells (abstract; p. 82, column 2, first full paragraph, as idiotype/GMCSF fusion proteins). Enhancers comprising enhancers from the human immunoglobulin κ locus, a promoter and polyadenylation site are taught at p. 83, column 1, second full paragraph; and especially Figure 1b, page 85, as immunoglobulin κE3' and κEi. Cytokine genes for IL-6, TNF, and GM-CSF are taught at p. 83, column 1, last paragraph; and Table 1. Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are taught at Figure 1b, page 85, including the hygromycin resistance gene (hygR) (see also Figure 1a, p. 84). Vectors preferably containing sequences derived from bacterial vectors (*i.e.* lacZ) are taught at p. 85, column 1. A vector construct wherein the marker gene lacks an enhancer or contains a non-functional enhancer is taught at p. 85, Figure 1b. Specific regions and base pair sequence length are taught in Figure 1.

Mocikat et al., (Immunology. 1995:84:159-163) teach a vector for homologous recombination at the Ig locus (Figure 1; paragraph bridging pages 159-160). Insertion vectors comprising a murine IgH locus including a 5' homology flank are taught at p. 160, column 2, third paragraph; Figure 1). Additionally, the vector contains a 2.3 kb fragment from the mouse μ

intron (Figure 1; and Figure 3, p. 161; see also p. 160, column 1, first full paragraph). Mocikat et al., explains that chimeric constructs can be used because of the ease and rapidity of manipulation circumventing the need to isolate variable (V) genes to perform selection schemes over periods of months and to use toxic drugs (abstract; p. 162, column 2, last paragraph).

Kardinal et al., (Eur J Immunol. 1995 Mar; 25(3):792-797, Abstract only), teach integration vectors for antibody chimerization by homologous recombination in hybridoma cells.

EP 0675203 (Mocikat, published 4 October 1995; machine translation into English provided by the examiner) teaches integration vectors for the production of genes encoding recombinant antibodies (translation, specification p. 1, paragraph 1).

DE 4406512 (Mocikat, published 16 February 1995, machine translation into English provided by the examiner) teaches integration vectors for producing genes which encode recombinant antibodies to vectors for producing recombinant antibodies.

Tao et al., (Nature. 1993 Apr 22;362(6422):755-8. Abstract only), teach that by fusing a well-characterized tumor specific antigen, which is an antibody corresponding to the specific idiotype expressed on a murine B cell lymphoma, to GM-CSF, the tumor-derived idiotype can be converted into a strong immunogen capable of inducing idiotype-specific antibodies and of protecting recipient animals from challenge with an otherwise lethal dose of tumor cells.

In the instant case, only one species of the claimed invention is disclosed in the specification (see pages 13-14 of the specification, labeled pages 17 and 18) as a vector comprising pSP72(ΔEV)-mGM-CSF (ΔL) cloned into pSVgpt-huγ1-A5. Other than Appellant's example of a vector comprising pSP72(ΔEV)-mGM-CSF (ΔL) cloned into pSVgpt-huγ1-A5, and the vectors taught in the art (*supra*) the skilled artisan, when considering the instant claims, is left to guess at the multiple vector components from which to pick and choose in order to construct vectors encompassed by the instant claims. Aside from Appellant's one example and the vectors taught in the art, there is no defined common structure for the claimed genus of vectors.

Instead, the instant claims and specification do nothing more than suggest various vector components in the form of generic lists or as a laundry list of potential components that one of ordinary skill in the art could piece together to obtain possession of the claimed genus of vectors. In this sense, the instant case is on point with *Rochester* and *Ex Parte Kubin* because all that has been disclosed is a description of how to obtain possession. See also, *Fujikawa v. Wattanasin*,

93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species). By way of illustration, possession of the Oxford English Dictionary does not mean that a skilled artisan can pick and choose known words to create the Collected Works of William Shakespeare.

The components of the claimed vector comprise nucleic acid sequences from a region of "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron" (see specifically, claim 1(a)). Simply knowing the nucleic acid code of a μ intron or κ intron is not sufficient to describe a representative number of species or to adequately show possession when the claim limitations, as written, recite that the "at least 1.5kb" segment is from a region which is homologous to an at least 1.5kb segment of the μ intron or the κ intron. The "homology" of the region is not limited to any particular portion of the μ intron or the κ intron. The linear nucleic acid sequence of the immunoglobulin κ locus, for example, is known. However, the skilled artisan would not be apprised that Appellant was in possession of a generic homologous region of a genus of κ introns without knowing something more about the structure of the homologous region required for the vector. The evidentiary art of record clearly shows that the large size of the κ locus makes it exceedingly difficult to determine which homologous intron segments structurally constitute the claimed region of "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron." The limited disclosures in the specification and the art do not remedy the inadequate descriptive support for possession of the claimed genus of vectors because the specification simply does not disclose a sufficient number of representative homologous region segments (species) of the various κ introns, such that the Appellant can show possession of the genus of vectors as claimed. Additionally, the claimed genus of vectors also encompasses at least one DNA sequence encoding a part of an immunoglobulin constant region (compare claim 1(b)). This limitation broadly reads on a dipeptide or even a single amino acid.

When considering whether Appellant has disclosed a sufficient representative number of species, the "representative number of species" means that the species which are adequately described are representative of the entire genus. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

See *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (holding that a subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads)). The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615. Further, in *The Regents of the University of California v. Eli Lilly and Co*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed Cir. 1997) the Court held that the written description requirement not satisfied by merely providing "a result that one might achieve if one made that invention"(see also *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming a rejection for lack of written description because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate")). It is an established tenet of patent law that possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord *Ex Parte Kubin*, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1).

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera of vectors to establish that Appellant was in possession of the vectors in their full scope. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera of vectors, including: vectors encoding a generic genus of cytokine-immunoglobulin fusion proteins; vectors comprising a generic genus of immunoglobulin structures; vectors comprising a genus of cytokines; vectors comprising a genus of marker genes; vectors comprising a genus of enhancers; vectors encoding a genus of unspecified nucleic acids that are homologous to a region comprising the Cμ or Cκ enhancer; vectors comprising a genus of generic bacterially compatible regulatory units; vectors comprising a generic DNA sequence from part of a constant region of an immunoglobulin; vectors comprising a genus of interleukins; vectors comprising a genus of interferons; vectors comprising a genus of colony-stimulating factors; vectors comprising a genus of lymphokines; vectors comprising a genus of growth factors; and vectors comprising unspecified homologous

regions from the mu or kappa introns of any species. One of skill in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genus at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Appellant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Appellant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7-9, 11, 13-17, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996), as evidenced by Mucke et al., (Gene Therapy. 1997 Feb;4:82-92).

The '449 patent teaches gene constructs of cytokine-immunoglobulin fusion proteins in malignant B-cells comprising enhancers from the immunoglobulin μ and κ locus, the immunoglobulin heavy chain μ locus, and the immunoglobulin λ locus, a promoter and polyadenylation site (see abstract, Figure 1; column 4, lines 30-67 to column 5, lines 1-58; and column 8, lines 1-30) (compare instant claims 1 and 29). μ and κ locus intron [*i.e.* non-functional] enhancers are taught at column 4, lines 37-54 (compare instant claims 1, 3, and 4). Immunoglobulin heavy chain μ locus is taught at column 4, line 54 (compare instant claim 1). An immunoglobulin κE3' region is taught at column 8, lines 29-30 (compare instant claim 1). κ locus exon enhancers [i.e. functional enhancers] are taught at column 4, line 38 (compare instant claims 1 and 2). Homologous regions comprising 2.6kb are taught at column 8, line 5 (compare instant claims 1(a), 7, and 8). Sequences encoding cytokine genes of interest are taught at column 4, lines 56-57 (compare instant claims 1 and 15). Specific cytokine genes for IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, GM-CSF, G-CSF, TNFα, MCP-1, and IFNγ are taught at column 5, lines 55-58, column 7, lines 45-47, column 8, lines 59-63, and column 9, line 64 (compare instant claims 1, 15, and 16). Marker genes that are selectable in eukaryotic B cells and contain a

functional enhancer region are taught at column 4, lines 59-60, and column 5, lines 21-26, including hygromycin resistance gene and a neomycin resistance gene (compare instant claims 1, 2, and 17). Vectors preferably containing sequences derived from bacterial vectors are taught at column 5, lines 15-16 (compare instant claims 1 and 9). A vector construct lacking the enhancer cassette and marker are taught at column 9, lines 2-4 (compare instant claims 1 and 5). Human immunoglobulin κ locus is taught at column 3, line 52 (compare instant claims 1, 7, 8, 11, 13, and 14). The '449 patent teaches the BC219-TNFα vector integrated into BL60 cells (EBV-positive human lymphoma cells) capable of expressing TNFα (column 9, lines 23-24; and Table 2) (compare instant claims 1 and 29). BL60 cells with integrated BC219GM-CSF and BC216-IL6 expressing GM-CSF and IL-6 respectively, are also taught in Table 2 (compare instant claims 1 and 29).

The '449 patent teaches "[a] gene construct containing, in functional association, at least: (a) (i) a combination of two enhancer elements of the immunoglobulin kappa locus, namely the kappa intron enhancer (kappa Ei) and the kappa 3' enhancer (kappa E3'); or (ii) a combination of two enhancer elements of the immunoglobulin heavy chain mu locus, namely mu Ei and the mu E3' enhancer region located 3' of C alpha; or (iii) a combination of one or more of these enhancer elements of (ii) together with one or more of the aforementioned elements of the immunoglobulin kappa locus" (column 4, line 39-42). The combination of kappa E3' and kappa Ei enhancers, as taught by the '449 patent exceeds the "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron."

Mucke et al., (cited for exemplary purpose only to demonstrate the inherent features of the vector in the '449 patent) demonstrates that kappa E3' is approximately 881bp long and kappa Ei is approximately 1486kb pairs long, as evidenced by the BC219 vector (p. 85, Figure 1). The combination of both kappa enhancer regions, as taught by the '449 patent and as visually evidenced by Mucke et al., meets the limitations of the instant claims comprising a homologous length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8). Polack, inventor of the '449 patent is a co-author of the Mucke et al., paper. The Mucke et al., paper shows the vector of the '449 patent in detail, as Figure 1.

Mucke et al., demonstrate vectors comprising gene constructs of cytokine fusion proteins expressed in malignant B-cells (abstract; p. 82, column 2, first full paragraph, as

idiotype/GMCSF fusion proteins). Enhancers comprising enhancers from the human immunoglobulin κ locus, a promoter and polyadenylation site are demonstrated at p. 83, column 1, second full paragraph; and especially Figure 1b, page 85, as immunoglobulin κE3' and κEi. Cytokine genes for IL-6, TNF, and GM-CSF are demonstrated at p. 83, column 1, last paragraph; and Table 1. Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are demonstrated at Figure 1b, page 85, including the hygromycin resistance gene (hygR) (see also Figure 1a, p. 84). Vectors preferably containing sequences derived from bacterial vectors *(i.e.* lacZ) are demonstrated at p. 85, column 1. A vector construct wherein the marker gene lacks an enhancer or contains a non-functional enhancer is demonstrated at p. 85, Figure 1b. Specific regions and base pair sequence length are taught in Figure 1.

The combination of kappa E3' and kappa Ei enhancers, as taught by the '449 patent and as evidenced in the BC219 vector of Figure 1 of Mucke et al., are homologous to an at least 1.5k segment of the κ intron. Mucke et al., evidences that kappa E3' is approximately 881bp long and kappa Ei is approximately 1486kb pairs long (p. 85, Figure 1). The combination of both kappa enhancer regions, as evidenced by Mucke et al., meets the limitations of the instant claims comprising a homologous length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9, 11-13, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996), Levy et al., US Patent 6,099,846 (8 August 2000, benefit to 14 April 1995), and Gillies et al., US Patent 5,650,150 (22 July 1997, benefit to 7 November 1991), as evidenced by Mucke et al., (Gene Therapy. 1997 Feb).

The '449 patent teaches gene constructs of cytokine-immunoglobulin fusion proteins in malignant B-cells comprising enhancers from the immunoglobulin μ and κ locus, the immunoglobulin heavy chain μ locus, and the immunoglobulin λ locus, a promoter and polyadenylation site (see abstract, Figure 1; column 4, lines 30-67 to column 5, lines 1-58; and column 8, lines 1-30) (compare instant claims 1 and 29). μ and κ locus intron [*i.e.* non-functional] enhancers are taught at column 4, lines 37-54 (compare instant claims 1, 3, and 4). Immunoglobulin heavy chain μ locus is taught at column 4, line 54 (compare instant claim 1). An immunoglobulin κE3' region is taught at column 8, lines 29-30 (compare instant claim 1). κ locus exon enhancers [i.e. functional enhancers] are taught at column 4, line 38 (compare instant claims 1 and 2). Homologous regions comprising 2.6kb are taught at column 8, line 5 (compare instant claims 1(a), 7, and 8). Sequences encoding cytokine genes of interest are taught at column 4, lines 56-57 (compare instant claims 1 and 15). Specific cytokine genes for IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, GM-CSF, G-CSF, TNFα, MCP-1, and IFNγ are taught at column 5, lines 55-58, column 7, lines 45-47, column 8, lines 59-63, and column 9, line 64 (compare instant claims 1, 15, and 16). Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are taught at column 4, lines 59-60, and column 5, lines 21-26, including hygromycin resistance gene and a neomycin resistance gene (compare instant claims 1, 2, and 17). Vectors preferably containing sequences derived from bacterial vectors are taught at column 5, lines 15-16 (compare instant claims 1 and 9). A vector construct lacking the enhancer cassette and marker are taught at column 9, lines 2-4 (compare instant claims 1 and 5). Human immunoglobulin κ locus is taught at column 3, line 52 (compare instant claims 1, 7, 8, 11, 13, and 14). The '449 patent teaches the BC219-TNFα vector integrated into BL60 cells (EBV-positive human lymphoma cells) capable of expressing TNFα (column 9, lines 23-24; and Table 2) (compare instant claims 1 and 29). BL60 cells with integrated BC219GM-CSF and BC216-IL6 expressing GM-CSF and IL-6 respectively, are also taught in Table 2 (compare instant claims 1 and 29).

The '449 patent teaches "[a] gene construct containing, in functional association, at least: (a) (i) a combination of two enhancer elements of the immunoglobulin kappa locus, namely the kappa intron enhancer (kappa Ei) and the kappa 3' enhancer (kappa E3'); or (ii) a combination of two enhancer elements of the immunoglobulin heavy chain mu locus, namely mu Ei and the mu

E3' enhancer region located 3' of C alpha; or (iii) a combination of one or more of these enhancer elements of (ii) together with one or more of the aforementioned elements of the immunoglobulin kappa locus" (column 4, line 39-42). The combination of kappa E3' and kappa Ei enhancers, as taught by the '449 patent exceeds the "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron."

The '449 patent does not specifically teach a DNA sequence encoding the constant region or a part of the constant region from a mouse immunoglobulin (compare instant claim 12).

The '150 patent teaches vectors for expression of recombinant antibody-cytokine fusion proteins produced in malignant B cells, including GM-CSF-Ig fusion proteins (abstract). . Mouse κ light chain 3' UTR sequences are taught at column 3, line 51. Vector sequences comprising DNA of mouse origin and human origin are taught at column 2, lines 55-67. See also. Column 2, lines 45-47.

The '846 patent teaches construction of an idiotype/GM-CSF fusion protein using murine B-cell tumor 38C13 cells and VH and VL genes of the 38C12 tumor cells ligated to human Igγ and Igκ constant region genes in the heavy and light-chain expression vectors pSV2-ΔHGPT and pSV184-ΔHneo (column 4, lines 50-67 to column 5, lines 1-24). Construction of the vectors is shown in detail in Figures 1A and 1B.

Mucke et al., (cited for exemplary purpose only to demonstrate the inherent features of the vector in the '449 patent) demonstrates that kappa E3' is approximately 881bp long and kappa Ei is approximately 1486kb pairs long, as evidenced by the BC219 vector (p. 85, Figure 1). The combination of both kappa enhancer regions, as taught by the '449 patent and as visually evidenced by Mucke et al., meets the limitations of the instant claims comprising a homologous length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8). Polack, inventor of the '449 patent is a co-author of the Mucke et al., paper. The Mucke et al., paper shows the vector of the '449 patent in detail, as Figure 1. Mucke et al., demonstrate vectors comprising gene constructs of cytokine fusion proteins expressed in malignant B-cells (abstract; p. 82, column 2, first full paragraph, as idiotype/GMCSF fusion proteins). Enhancers comprising enhancers from the human immunoglobulin κ locus, a promoter and polyadenylation site are demonstrated at p. 83, column 1, second full paragraph; and especially Figure 1b, page 85, as immunoglobulin κE3' and κEi. Cytokine genes for IL-6, TNF, and GM-CSF are demonstrated at

p. 83, column 1, last paragraph; and Table 1. Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are demonstrated at Figure 1b, page 85, including the hygromycin resistance gene (hygR) (see also Figure 1a, p. 84). Vectors preferably containing sequences derived from bacterial vectors (*i.e.* lacZ) are demonstrated at p. 85, column 1. A vector construct wherein the marker gene lacks an enhancer or contains a non-functional enhancer is demonstrated at p. 85, Figure 1b. Specific regions and base pair sequence length are taught in Figure 1.

The combination of kappa E3' and kappa Ei enhancers, as taught by the '449 patent and as evidenced by the BC219 vector of Figure 1b of Mucke et al., are homologous to an at least 1.5k segment of the κ intron. Mucke et al., evidences that kappa E3' is approximately 881bp long and kappa Ei is approximately 1486kb pairs long (p. 85, Figure 1). The combination of both kappa enhancer regions, as evidenced by Mucke et al., meets the limitations of the instant claims comprising a homologous length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8).

In view of the facts recited above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention, as set forth above.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the instant invention to combine the teachings of the '449, the '846, and the '150 patents, as evidenced by Mucke et al. The person of ordinary skill in the art could have combined the elements as claimed by known methods to produce a vector capable of expressing an immunoglobulin-cytokine fusion protein in malignant B cells, using a constant region from a mouse, as taught by the '150 patent. It would have been obvious and predictable to merely combine or substitute at least one DNA sequence encoding a part of a mouse constant region in the vector construct for the human constant region with predictable results because of similarities in mouse and human constant regions, which are old and well known in the art.

Additionally, the limitation of at least one DNA sequence encoding a part of an immunoglobulin constant region (compare claims 12 and 1(b)) broadly reads on a dipeptide or even a single amino acid. The '150 patent provides the motivation for the combination because

it teaches vectors for expression of recombinant antibody-cytokine fusion proteins produced in malignant B cells, including GM-CSF-Ig fusion protein, in which mouse κ light chain 3' UTR sequences are used. Further, vector sequences comprising DNA of mouse origin and human origin are also taught. Both the level of skill in the art in the field of molecular biology in vector construction and the actual construction of vectors by the '449 patent, as evidenced by Mucke et al., and the vector constructions of the '486 and '150 patents make the substitution predictable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Polack et al., US Patent 6,521,449 (18 February 2003, benefit to 12 September 1996), Mocikat et al., (Immunology. 1995:84:159-163), and Mucke et al., (Gene Therapy. 1997 Feb;4:82-92).

The '449 patent teaches gene constructs of cytokine-immunoglobulin fusion proteins in malignant B-cells comprising enhancers from the immunoglobulin μ and κ locus, the immunoglobulin heavy chain μ locus, and the immunoglobulin λ locus, a promoter and polyadenylation site (see abstract, Figure 1; column 4, lines 30-67 to column 5, lines 1-58; and column 8, lines 1-30) (compare instant claims 1 and 29). μ and κ locus intron [*i.e.* non-functional] enhancers are taught at column 4, lines 37-54 (compare instant claims 1, 3, and 4). Immunoglobulin heavy chain μ locus is taught at column 4, line 54 (compare instant claim 1). An immunoglobulin κE3' region is taught at column 8, lines 29-30 (compare instant claim 1). κ locus exon enhancers [i.e. functional enhancers] are taught at column 4, line 38 (compare instant claims 1 and 2). Homologous regions comprising 2.6kb are taught at column 8, line 5 (compare instant claims 1(a), 7, and 8). Sequences encoding cytokine genes of interest are taught at column 4, lines 56-57 (compare instant claims 1 and 15). Specific cytokine genes for IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, GM-CSF, G-CSF, TNFα, MCP-1, and IFNγ are taught at column 5, lines

55-58, column 7, lines 45-47, column 8, lines 59-63, and column 9, line 64 (compare instant claims 1, 15, and 16). Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are taught at column 4, lines 59-60, and column 5, lines 21-26, including hygromycin resistance gene and a neomycin resistance gene (compare instant claims 1, 2, and 17). Vectors preferably containing sequences derived from bacterial vectors are taught at column 5, lines 15-16 (compare instant claims 1 and 9). A vector construct lacking the enhancer cassette and marker are taught at column 9, lines 2-4 (compare instant claims 1 and 5). Human immunoglobulin κ locus is taught at column 3, line 52 (compare instant claims 1, 7, 8, 11, 13, and 14). The '449 patent teaches the BC219-TNFα vector integrated into BL60 cells (EBV-positive human lymphoma cells) capable of expressing TNFα (column 9, lines 23-24; and Table 2) (compare instant claims 1 and 29). BL60 cells with integrated BC219GM-CSF and BC216-IL6 expressing GM-CSF and IL-6 respectively, are also taught in Table 2 (compare instant claims 1 and 29). The '449 patent teaches "[a] gene construct containing, in functional association, at least: (a) (i) a combination of two enhancer elements of the immunoglobulin kappa locus, namely the kappa intron enhancer (kappa Ei) and the kappa 3' enhancer (kappa E3'); or (ii) a combination of two enhancer elements of the immunoglobulin heavy chain mu locus, namely mu Ei and the mu E3' enhancer region located 3' of C alpha; or (iii) a combination of one or more of these enhancer elements of (ii) together with one or more of the aforementioned elements of the immunoglobulin kappa locus" (column 4, line 39-42). The combination of kappa E3' and kappa Ei enhancers, as taught by the '449 patent exceeds the "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron."

The '449 patent does not specifically teach a DNA sequence encoding the constant region or a part of the constant region from a mouse immunoglobulin (compare instant claim 12).

Mocikat et al., teach a vector for homologous recombination at the Ig locus (Figure 1; paragraph bridging pages 159-160) comprising a murine IgH locus including a 5' homology flank (at p. 160, column 2, third paragraph; Figure 1) (compare instant claims 1(b) and 12). Additionally, the vector contains a 2.3 kb fragment from the mouse μ intron (Figure 1; and Figure 3, p. 161; see also p. 160, column 1, first full paragraph). Mocikat et al., explains that chimeric constructs can be used because of the ease and rapidity of manipulation circumventing

the need to isolate genes to perform selection schemes over periods of months and to use toxic drugs (abstract; p. 162, column 2, last paragraph).

Mucke et al., teaches vectors comprising gene constructs of cytokine fusion proteins expressed in malignant B-cells (abstract; p. 82, column 2, first full paragraph, as idiotype/GMCSF fusion proteins). Enhancers comprising enhancers from the human immunoglobulin κ locus, a promoter and polyadenylation site are demonstrated at p. 83, column 1, second full paragraph; and especially Figure 1b, page 85, as immunoglobulin κE3' and κEi. Cytokine genes for IL-6, TNF, and GM-CSF are taught at p. 83, column 1, last paragraph; and Table 1. Marker genes that are selectable in eukaryotic B cells and contain a functional enhancer region are taught at Figure 1b, page 85, including the hygromycin resistance gene (hygR) (see also Figure 1a, p. 84). Vectors preferably containing sequences derived from bacterial vectors (*i.e.* lacZ) are taught at p. 85, column 1. A vector construct wherein the marker gene lacks an enhancer or contains a non-functional enhancer is taught at p. 85, Figure 1b. Specific regions and base pair sequence length are taught in Figure 1. The combination of kappa E3' and kappa Ei enhancers, as taught by the BC219 vector of Figure 1 of Mucke et al., are "homologous to an at least 1.5k segment of the κ intron." Mucke et al., teach that kappa E3' is approximately 881bp long and kappa Ei is approximately 1486kb pairs long (p. 85, Figure 1). The combination of kappa E3' and kappa Ei enhancers, as taught by the '449 patent and as exemplified in the BC219 vector of Figure 1 of Mucke et al., are "homologous to an at least 1.5k segment of the κ intron." The combination of both kappa enhancer regions, as taught by Mucke et al., meets the limitations of the instant claims comprising a homologous length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8).

In view of the facts recited above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results. The prior art teaches all of the limitations of the claimed invention, as set forth above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to create a vector capable of expressing an immunoglobulin-cytokine fusion protein in malignant B cells, as taught by the '449 patent and Mucke et al., using at least one DNA sequence encoding part of a mouse immunoglobulin constant region, such as the

5'homology flank from the IgH locus, as taught by Mocikat, with predictable results. The limitation of the vector comprising at least one DNA sequence encoding a part of a mouse immunoglobulin constant region (compare claims 12 and 1(b)) broadly reads on a dipeptide or even a single amino acid. It would have been obvious and predictable to merely combine or substitute at least one DNA sequence encoding a part of a mouse constant region in the vector construct for the human constant region with predictable results because of similarities in mouse and human constant regions, which are old and well known in the art.

Additionally, Mucke et al, and the '449 patent, teach all of the components of the vector, including a DNA sequence encoding immunoglobulin domains from a human. Mocikat teaches vector constructs using a DNA sequence encoding a part of a mouse immunoglobulin 5' flank constant. Mocikat provides the rationale/motivation for combination of the references because a chimeric vector would result in constructs that would be easier to use due to the rapidity of manipulation, time savings, and not having to engage in toxic drug selection (p. 162, column 2, last paragraph).

(10) Response to Arguments

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

The central issue is whether the claimed genera of vectors is sufficiently described such that one of skill in the art would be apprised that Appellant was in possession of the genera.

Appellant argues (Brief, page 6) that as of the effective filing date of the application, all of the common components of the claimed vector, μ or κ intron sequences, immunoglobulin constant region sequences, cytokine sequences, selectable marker sequences, and enhancer sequences were well known and available to a person of ordinary skill in the art. Appellant argues that an artisan, upon reading the present disclosure, would reasonably conclude that the inventor had in his possession the components and therefore the claimed vector.

Appellant argues that the instant fact pattern is very different from that of *Rochester* of [*Ex Parte*] *Kubin* because in *Rochester*, the COX-2 inhibitors were neither known in the art nor named in the application. In [*Ex Parte*] *Kubin*, none of the exemplary NAIL sequences included any variation within the reference amino acid sequence. The Board ruled that the exemplary species did not sufficiently represent the claimed genus. In contrast to *Rochester* or [*Ex Parte*]

Kubin, the genera of μ or κ intron sequences, immunoglobulin constant region sequences, cytokine sequences, selectable marker sequences, or enhancer sequences were well known in the art. Appellant argues that the examiner's analysis of "representative number of species" or "common structural features" and conclusion pertaining to a patent Appellant's attempt to broadly claim a genus of previously unknown species thus have no relevance in the written description assertion in this application.

Appellant argues that the large number of possible selections within each genus of known components is evidence of a broad scope of enablement and possession of the invention, but is not "remotely akin" to the hunting for the unknown referred to by the Supreme Court in *Brenner v. Manson*, 148 USPQ 689 (S. Ct. 1966). Appellant argues that one's ability to choose from a broad range of known components to practice a claimed invention supports the conclusion of the inventor having possession of the invention.

Appellant's arguments have been fully considered, but they are not persuasive for the following reasons. The components of the claimed vector comprise nucleic acid sequences from a region of "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron" (see specifically, claim 1(a)). Simply knowing the linear nucleic acid sequence of a μ intron or κ intron is not sufficient to describe which homologous region(s) Appellant is claiming. Even though the linear nucleic acid sequence of the immunoglobulin κ locus (for example) is known, the skilled artisan would not readily be apprised that Appellant was in possession of the claimed genus of vectors comprising regions which include generically homologous nucleic acid sequences from a region of "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron."

The prior art of record clearly shows that the large size of the κ locus, for example, makes it exceedingly difficult to determine which "homologous" segments may constitute the claimed region of "at least 1.5kb. The "homology" of the region is not limited to any particular portion of the μ intron or the κ intron. The linear nucleic acid sequence of the immunoglobulin κ locus, for example, is known. However, the skilled artisan would not be apprised that Appellant was in possession of a generic homologous region of a genus of κ introns without knowing something more about the structure of the homologous region required for the vector. The evidentiary art of record clearly shows that the large size of the κ locus makes it exceedingly difficult to determine

which homologous intron segments structurally constitute the claimed region of "at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or the κ intron." The limited disclosures in the specification and the art do not remedy the inadequate descriptive support for possession of the claimed genus of vectors because the specification simply does not disclose a sufficient number of representative homologous region segments (species) of the various κ introns, such that the Appellant can show possession of the genus of vectors as claimed. Additionally, the claimed genus of vectors also encompasses at least one DNA sequence encoding a part of an immunoglobulin constant region (compare claim 1(b)). This limitation broadly reads on a dipeptide or even a single amino acid.

The instant claims and specification do nothing more than suggest various vector components in the form of generic lists or as a laundry list of potential components that one of ordinary skill in the art could piece together to obtain possession of the claimed genus of vectors. In this sense, the instant case is on point with *Rochester* and *Ex Parte Kubin* because all that has been disclosed is a description of how to obtain possession. See also, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera of vectors to establish that Appellant was in possession of the vectors in their full scope. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genera of vectors, including: vectors encoding a generic genus of cytokine-immunoglobulin fusion proteins; vectors comprising a generic genus of immunoglobulin structures; vectors comprising a genus of cytokines; vectors comprising a genus of marker genes; vectors comprising a genus of enhancers; vectors encoding a genus of unspecified nucleic acids that are homologous to a region comprising the Cμ or Cκ enhancer; vectors comprising a genus of generic bacterially compatible regulatory units; vectors comprising a generic DNA sequence from part of a constant region of an immunoglobulin; vectors comprising a genus of interleukins; vectors comprising a genus of interferons; vectors comprising a genus of colony-stimulating factors; vectors comprising a genus of lymphokines;

vectors comprising a genus of growth factors; and vectors comprising unspecified homologous regions from the mu or kappa introns of any species. One of skill in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genus at the time the application was filed. One of skill in the art would not recognize from the disclosure that the Appellant was in possession of the claimed genera at the time the application was filed.

Claim Rejections - 35 USC § 102(e)

The central issue is whether the limitation of "a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or κ intron" recited in claim 1(b) is met by the combination of two enhancer κ intron elements that are homologous to the κ intron, and which provide a combined length of 2.64kb, but individually are each less than 1.5kb in length.

Appellant argues (Brief, page 9) that the Polack reference and Mucke reference describe expression vectors that contain a promoter as well as a polynucleotide sequence encoding the polypeptide to be expressed from the vectors. However, Appellant argues that neither Polack nor Mucke provides all of the limitations of the pending claims. Appellant argues that the limitation of "a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or κ intron" cannot be found in either of the two references. Appellant argues that, as the examiner has acknowledged, Polack teaches the combined use of two enhancer κ intron elements, which provide a combined length of over 1.5kb, but each is less than 1.5kb. Appellant argues that because neither Polack nor Mucke provides the limitation of "a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or κ intron," there is no basis for the anticipation rejection.

Appellant's arguments have been fully considered, but they are not persuasive for the following reasons. The claims, as written, do not require that the "homologous" region "to an at least 1.5kb segment of the μ intron or the κ intron" be continuous. Instead, the "homologous" region may be comprised of a multiplicity of segments so long as they are homologous to the μ intron or the κ intron and when placed into the claimed vector are a total of at least 1.5kb in length.

Appellant places emphasis on the word "continuous" in the claims. When the gene segments are placed together in a vector, they will innately be continuous with one another. However, the claim limitation of "continuous," as written, does not limit the homologous region to being continuous segments from the μ intron or the κ intron that are each individually at least 1.5kb in length.

The '449 patent, as evidenced by Mucke et al., teaches that two distinct pieces of the κ intron, when pieced together in a vector, comprise a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the κ intron, meeting the limitations of the claims as written. The combination of both kappa intron enhancer regions, as taught by the '449 patent and as visually evidenced by Mucke et al. (Figure 1b), meets the limitations of the instant claims, comprising a homologous kappa intron length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8). Additionally, once placed in the vector, the 2.64kb homologous region is continuous with the other regions in the vector, as taught by the '449 patent and visually evidenced by Mucke et al., in Figure 1(b). The vector of the '449 patent and Mucke et al., work and are functional with the combined 2.64kb homologous segment.

Claim Rejections - 35 USC § 103(a)

Over Polack (as evidenced by Mucke), Gillies, and Levy

The central issue is whether the limitation of "a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or κ intron" recited in claim 1(b) is met by the combination of two enhancer κ intron elements that are homologous to the κ intron, and which provide a combined length of 2.64kb, but individually are each less than 1.5kb in length.

Appellant argues that there must be a suggestion or motivation in the art for one of ordinary skill in the art to combine the limitations and there must be a reasonable expectation of success in making the combination. Appellant refers to arguments discussed in the section related to the rejection under 35 USC 102(e) and argues that the primary references Polack and Mucke relate to expression vectors and do not provide at least one limitation of the pending claims, namely "a continuous region of at least 1.5kb that is homologous to an at least 1.5kb segment of the μ intron or the κ intron." Appellant argues that the Levy and Gillies references do

not supplement the missing limitations of the "a continuous region of at least 1.5kb that is homologous to an at least 1.5kb segment of the μ intron or the κ intron" and therefore no *prima facie* obviousness can be established.

Appellant's arguments have been fully considered, but they are not persuasive for the following reasons. The Levy and Gillies references do not need to supplement limitations which are taught by the '449 patent, as evidenced by Mucke et al. The claims, as written, do not require that the "homologous" region "to an at least 1.5kb segment of the μ intron or the κ intron" be continuous. Instead, the "homologous" region may be comprised of a multiplicity of segments so long as they are homologous to the μ intron or the κ intron and when placed into the claimed vector are a total of at least 1.5kb in length.

Appellant places emphasis on the word "continuous" in the claims. When the gene segments are placed together in a vector, they will innately be continuous with one another. However, the claim limitation of "continuous," as written, does not limit the homologous region to being continuous segments from the μ intron or the κ intron that are each individually at least 1.5kb in length.

The '449 patent, as evidenced by Mucke et al., teaches that two distinct pieces of the κ intron, when pieced together in a vector, comprise a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the κ intron, meeting the limitations of the claims as written. The combination of both kappa intron enhancer regions, as taught by the '449 patent and as visually evidenced by Mucke et al. (Figure 1b), meets the limitations of the instant claims, comprising a homologous kappa intron length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8). Additionally, once placed in the vector, the 2.64kb homologous region is continuous with the other regions in the vector, as taught by the '449 patent and visually evidenced by Mucke et al., in Figure 1(b). The vector of the '449 patent and Mucke et al., work and are functional with the combined 2.64kb homologous segment.

Claim Rejections - 35 USC § 103(a)

Over Mucke, Polack, and Mocikat

The central issue is whether the limitation of "a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the μ intron or κ intron" recited in claim 1(b) is

met by the combination of two enhancer κ intron elements that are homologous to the κ intron, and which provide a combined length of 2.64kb, but individually are each less than 1.5kb in length.

Appellant refers to arguments discussed in the section related to the rejection under 35 USC 103(a) [and by inference 35 USC 102(e)] and argues that the primary references Polack and Mucke relate to expression vectors and do not provide at least one limitation of the pending claims, namely "a continuous region of at least 1.5kb that is homologous to an at least 1.5kb segment of the μ intron or the κ intron."

Appellant argues that the Mocikat reference is cited to provide the teaching of a vector for homologous recombination at the Ig locus. Appellant argues that because there is a fundamental difference in the purpose and mechanism of action between expression vectors (*e.g.,* the Polack vector) and integration vectors (*e.g.* the Mocikat vector), there would be no motivation to combine the teachings of the Polack and Mocikat references. Appellant argues that the advantages in protein expression that the examiner has alleged would relate solely to the expression of rearranged genomic sequence resulting from homologous recombination and genomic integration, crucial for an integration vector to effectuate gene expression as intended. Appellant argues that the recombination/integration process, however, is completely irrelevant to the direct expression of a recombinant protein, which is how an expression vector such as the Polack recombinants. Therefore, the advantages of the 2.3kb mouse μ intron fragment present in Mocikat's integration vector will not provide any motivation for a skilled artisan too use the fragment in Polack's expression vector.

Appellant argues that the combination of Polack, Mucke, and Mocikat together, teach away from replacing the enhancers used by Polack with the 2.3kb μ intron sequence used by Mocikat to modify Polack's expression vector because the Polack vector is an expression vector and uses enhancers to promote the expression of a coding sequence carried by the vector. Appellant argues that replacing the enhancers with the 2.3kb intron sequence would completely defeat the purpose of enhancing/promoting expression. Appellant argues that accordingly, there is at least one strong incentive for the skilled artisan not to combine Polack, Mucke, and Mocikat. Appellant argues that because the references are a "teaching away" from the claimed invention, no *prima facie* case of obviousness can be established.

Appellant's arguments have been fully considered, but they are not persuasive for the following reasons. With regard to Appellant's argument drawn to the recited "continuous region" in claim 1(b), the claims, as written, do not require that the "homologous" region "to an at least 1.5kb segment of the μ intron or the κ intron" be continuous. Instead, the "homologous" region may be comprised of a multiplicity of segments so long as they are homologous to the μ intron or the κ intron and when placed into the claimed vector are a total of at least 1.5kb in length. Appellant places emphasis on the word "continuous" in the claims. When the gene segments are placed together in a vector, they will innately be continuous with one another. However, the claim limitation of "continuous," as written, does not limit the homologous region to being continuous segments from the μ intron or the κ intron that are each individually at least 1.5kb in length. The '449 patent, as evidenced by Mucke et al., teaches that two distinct pieces of the κ intron, when pieced together in a vector, comprise a continuous region of at least 1.5kb which is homologous to an at least 1.5kb segment of the κ intron, meeting the limitations of the claims as written. The combination of both kappa intron enhancer regions, as taught by the '449 patent and as visually evidenced by Mucke et al. (Figure 1b), meets the limitations of the instant claims, comprising a homologous kappa intron length of approximately 2.64kb, combined (compare instant claims 1(a), 2, 3, 7, and 8). Additionally, once placed in the vector, the 2.64kb homologous region is continuous with the other regions in the vector, as taught by the '449 patent and visually evidenced by Mucke et al., in Figure 1(b). The vector of the '449 patent and Mucke et al., work and are functional with the combined 2.64kb homologous segment.

With regard to Appellant's argument that because there is a fundamental difference in the purpose and mechanism of action between expression vectors (*e.g.,* the Polack vector) and integration vectors (*e.g.* the Mocikat vector), there would be no motivation to combine the teachings of the Polack and Mocikat references, Appellant's arguments have been fully considered, but they are not persuasive. There is no evidence of a difference in the purpose between the vector of the '449 patent, as evidenced by Mucke et al., and the Mocikat vector. The vectors of the '449 patent and Mucke et al., are EBV-related vectors containing the Epstein-Barr virus nuclear antigen 1 gene and the EBV oriP, Epstein-Barr virus latent origin of replication gene. These genes are among the critical genes for creating integration vectors. The inclusion of these genes show that the vectors of the '449 patent and Mucke et al., are designed

to integrate into host DNA and express proteins of interest. See the '449 patent at column 5, lines 11-35; column 3, lines 6-42; Figure 1; and Example 2 (column 9). The vectors of the '449 patent are taught as preferably containing sequences derived from EBV vectors, including preferentially additionally containing the EBNA1 expression cassette (column 5, lines 11-21). See also, Mucke et al., at Figure 1(b), which clearly shows the EBNA1 expression cassette. The Mocikat vectors are taught as both integration as homologous recombination vectors (abstract).

With regard to Appellant's arguments that:(a) the recombination/integration process is irrelevant to the direct expression of a recombinant protein and that the advantages of the 2.3kb mouse μ intron fragment present in Mocikat's integration vector will not provide any motivation for a skilled artisan too use the fragment in Polack's expression vector; (b) that the combination of Polack, Mucke, and Mocikat together, teach away from replacing the enhancers used by Polack with the 2.3kb μ intron sequence used by Mocikat to modify Polack's expression vector because the Polack vector is an expression vector and uses enhancers to promote the expression of a coding sequence carried by the vector; and (c) that replacing the enhancers with the 2.3kb intron sequence would completely defeat the purpose of enhancing/promoting expression, Appellant's arguments have been fully considered, but they are not persuasive. The Mocikat reference was cited against the limitations of claim 12, which is dependent on claim 1, and recites that the DNA sequence of (b) encodes the constant region of a mouse. Claim 1(b) recites the limitation of at least one DNA sequence encoding a constant region of an immunoglobulin or a part of the constant region. Mocikat et al., teach a vector comprising a murine IgH locus including a 5' homology flank (p. 160, column 2, third paragraph; Figure 1) (compare instant claims 1(b) and 12). Mocikat et al., teaches vector constructs using a DNA sequence encoding portions of immunoglobulin constant domains from a mouse (compare instant claims 1(b) and 12). Mocikat et al., provides the rationale and motivation for combining the references in order to create expression vectors capable of producing an immunoglobulin-cytokine gene construct comprising chimeric domains because it would result in constructs that would be easier to use due to the rapidity of manipulation, time savings, and not having to engage in toxic drug selection (p. 162, column 2, last paragraph).

With regard to Appellant's argument that the references are a "teaching away" from the claimed invention and no *prima facie* case of obviousness can be established, Appellant's

argument has been fully considered, but it is not persuasive. As stated above, the Mocikat reference was cited against claim 12, which is dependent on claim 1 and recites that the DNA sequence of (b) encodes the constant region of a mouse (see above). The limitation of the vector comprising at least one DNA sequence encoding a part of a mouse immunoglobulin constant region (compare claims 12 and 1(b)) broadly reads on a dipeptide or even a single amino acid. Mocikat et al., teaches vector constructs using a DNA sequence encoding a part of an immunoglobulin constant domains from a mouse (compare instant claims 1(b) and 12). Mocikat et al., provides the rationale and motivation for combining the references in order to create expression vectors capable of producing an immunoglobulin-cytokine gene construct comprising chimeric domains because it would result in constructs that would be easier to use due to the rapidity of manipulation, time savings, and not having to engage in toxic drug selection (p. 162, column 2, last paragraph). Accordingly, the combination of references do not teach away from the claimed invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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